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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/014,812	12/14/2001	Stephen Palmer	PALMER=1	1664

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EXAMINER	
LIU, SAMUEL W	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/014,812	PALMER ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *7-27,29 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5-9-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 1-30 are pending.

Election/restriction

Applicants' election of Group I, claims 1-6 and 28-30, and election of ovulation induction agent, i.e., Piclamilast, in the response filed 19 March 2004without traverse is acknowledged. Yet, applicants present a traverse with respect to "additional election under 35 USC 121" of the Office action mailed 20 February 2004; the traverse is based on the ground that the compounds recited in claims 28-30 all are phosphodiesterase (PDE) inhibitors which are cAMP modulator, and that it should be allowed to encompass a class of compounds, i.e., PDE inhibitors that are used for inducing ovulation (see page 2).

Applicants' traverse has been considered but it is found to be not persuasive. First, the compounds recited in the instant claims are highly diverse in structure, e.g., cipamfylline is distinct from elected compound Piclamilast (i.e., RP 73401) (see reference A and Stevens, J. C. et al. (1997) *J. Pharmacol. Exp. Therapeu.* 282, 1389-1495). Since the structures of the PDE inhibitory compounds are highly diverse, it would be serous burden to Examiner to conduct separate search of the patent and nonpatent technical literature as well as a separate search in the nonpatent technical literature protein databases. Second, the instant application is directed to a method of ovulation induction comprising administering to a subject an organic compound of regulating cAMP level in said subject; wherein the said compound particularly is a PDE inhibitor. It has been demonstrated that PDE3 specific inhibitor blocks oocytes maturation; thus, inhibits the subsequent ovulation (see claims 1-3 and 14, and columns 3-4 and example 4 of US

Pat. No. 6110471). Thus, PDE3-specific inhibitor will not induce ovulation. The compound, milrinone (recited in claim 29) is such PDE3 specific inhibitor (see abstract of Zhang, W. et al. (2002) *Mol. Pharmacol.*, 62, 514-520). Therefore, the compounds recited in claims 28-30 are not encompassed in a class compound which has the same ability of inducing ovulation.

Thus, the requirement is still deemed proper and is therefore made FINAL.

Claims 7-27 and 29-30 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Note that inasmuch as claims 29-30 do not recite the elected Piclamilast compound, the claims are considered non-elected.

Therefore, elected claims 1-6 and 28 and elected compound, i.e., Piclamilast, are under examination to the extent that they are drawn to the elected invention.

IDS

The references of IDS filed 9 May 2002 have been considered.

Specification/Claim/ Objections

The disclosure is objected to because of the following informalities:

In page 7, line 5, "PDE" should be spelled out in full for the first instance of use. Seee also page 6, line 16, "hCG"; and page 48, line 20, "RIA".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not describe (i) all phosphodiesterase (PDE) inhibitors have ability of inducing ovulation; the specification only describes and provides working examples for PDE subtype 4 (i.e., PDE4) inhibitors (e.g., compounds 1-4 in Examples 1-8) have said ability; and (ii) modulator, which includes inhibitor and stimulator, of cAMP level for inductions of ovulation.

Thus, applicants are not in possession of a method of inducing ovulation comprising administering to a subject a non-polypeptide cAMP level modulator, or a PDE inhibitor. Applicants are in possession of the method of inducing ovulation comprising administering to a subject a PDE4 specific inhibitor.

There are 11 PDE subtypes; of them, PDE 4 and PDE 7 are cAMP specific (i.e., specifically hydrolyzes cAMP phosphodiester bond) while PED4 is only cAMP specific; By contrast, PDE5 and 6 are cGMP specific (see Table 1 of Travadi, J. N. et al. (2003) *Pediat. Pulmonol.* 36, 529-535). Because (i) structure and function of PDE superfamily is of complexity (see Conti, M. (2000) *Mol. Endocrinol.* 14, 1317-1327) and PDE activity is highly diverse; (ii) the PDE substrates, i.e., cGMP and cAMP involve in distinct cell signalings, and (iii) the current invention is unrelated to modulation of cGMP level in the subject, applicants need to provide written description for inhibitors of the PDE superfamily in order for enablement for the claimed method. Moreover, Conti et al. (US Pat. No. 6110471) have shown that the PDE3-specific

inhibitor prevents oocytes maturation thereby inhibits ovulation (see the patent claims 1-3 and 14 and columns 3-4), i.e., the PDE3 specific inhibitor has the opposite role in ovulation compared to PDE4 specific inhibitor. This indicates that not all PDE inhibitors have ability of inducing ovulation. Thus, without written description, one cannot know a compound inhibiting a PDE (e.g., PDE3) can elevate a cAMP level; thereby promote ovulation induction. Therefore, applicants are not in possession of the method of inducing ovulation comprising administering to a subject a PDE inhibitor (*a genus*) that encompasses any inhibitors of PDE subtypes, i.e., PDE1 to PDE3 and PDE5 to PDE11.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-6 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "modulator"; the recitation is not apparent as to whether or not the modulator refers to (i) stimulator or inhibitor of cAMP level; and (ii) partial stimulator of cAMP level in light of that some compounds are PDE dual inhibitor (e.g., Org20241 is PDE3/PED4 dual inhibitor). The dependent claims are also rejected.

Claim 3 recites "phosphodiesterase 4 isoform"; the recitation appears to be encompass subtypes of phosphodiesterase 4; the specification does not define any subtypes thereof. Thus, the recitation renders the claim indefinite.

Claim 28 contains the trademark/trade names "Ariflo®". Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe the matrix material used in the claimed process and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martins, T. J. et al. (US Pat. No. 6423710) and further in view of Garvey, D. S. et al. (US Pat No. 5958926).

Martins et al. teach 94 non-polypeptide PDE4 inhibitors in the table (see columns 200-202). At column 203, lines 23-26, Martin et al. teach it is well known that PDE4 inhibitors, e.g., rolipram (see claim 28) increases cAMP levels. Martin et al. teach a method of modulating cAMP level in a mammal (see column 19, lines 1-2). Martin et al. demonstrate that PDE4 inhibitors reduce serum TNFα levels in LPS-injected mice (column 203, lines 25-30). At column 1, lines 21-26, Martins et al. state that PDE4 inhibitors can be used to elevate cAMP level; and at column 21, lines 3-6, Martins et al. state that the PDE4 inhibitors elevate cAMP levels within granulose cells and thereby promote gonadotropin induction of ovulation.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to induce ovulation by administering to a female in need PDE4 inhibitor (e.g., Piclamilast as taught by Garvey et al. (see column 9, lines 11-14)), because Martins et al. teach that PDE4 inhibitors are routinely used to increasing cAMP levels and thus will be useful in the induction of ovulation, which is applied to the claims 1-3 and 28 of the instant application. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Claims 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martins, T. J. et al. (US Pat. No. 6423710) taken with Corbin A. (US Pat. No. 4338305), Zohar, Y. (US Pat. No. 5643877) and Bowman, W. C. et al. (in "*Texbook of Pharmacology*", the 2nd edition (1980), pages 20.20-20.21, Blackwell Scientific Publication), and further in view of Travadi, J. N. et al. (2003) *Pediat. Pulmonol.* 36, 529-535).

Martins et al. teach 94 non-polypeptide PDE4 inhibitors in the table (see columns 200-202). At column 203, lines 23-26, Martin et al. teach it is well known that PDE4 inhibitors, e.g., rolipram (see claim 28) increases cAMP levels. Martin et al. teach a method of modulating cAMP level in a mammal (see column 19, lines 1-2). Martin et al. demonstrate that PDE4 inhibitors reduce serum TNFα levels in LPS-injected mice (column 203, lines 25-30). At column 1, lines 21-26, Martins et al. state that PDE4 inhibitors can be used to elevate cAMP level; and at column 21, lines 3-6, Martins et al. state that the PDE4 inhibitors elevate cAMP levels within granulose cells and thereby promote gonadotropin induction of ovulation.

Yet, Martin et al. et al. do not explicitly teach at which point in the ovulatory cycle to administer the PDE4 inhibitors.

Zohar et al. teach administering a compound, a gonadotropin releasing hormone to induce ovulation in a female subject (see column 6, lines 5-9).

Corbin teaches that ovulation can be induced in the female mammal at a time *prior to* normal ovulation (see column 6, lines 38-39). At Figure 20.17, Bowman et al. illustrate ovulation occurs before secretary phase, i.e., luteal phase (se page 20.21, the right column, 2nd line). Thus, the Corbin's teaching actually indicates that ovulation is induced at least *prior to* the luteal phase.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the non-polypeptide cAMP level modulator, i.e., PDE4 inhibitor prior to the luteal phase of the host's ovulatory cycle. This is because (i) Zoher et al. teach administering a compound for ovulation induction, and Martin et al. teach that this compound is PDE4 inhibitors; (ii) Martins et al. further suggest that the PDE4 inhibitors are useful for ovulation induction and teach that the PDE4 inhibitors induce ovulation by the mechanism of enhancing gonadotropin induction of ovulation as they are cAMP level enhancer (see column 21, lines 3-6); (iii) of all eleven currently known isoforms of PDE enzymes, PED4 is only cAMP specific (see Table 1 of Travadi et al.); this is important because PDE3 inhibitor has opposite effect on ovulation; and (iv) Corbin and Bowman teachings indicate that ovulation induction should be carried out *prior to* the luteal phase. Therefore, the above are applied to the instant claims 4-6; the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER

Samuel Wei Liu, Ph.D.

Art Unit 1653, Examiner

April 27, 2004